

(19) World Intellectual Property  
Organization  
International Bureau



26 APR 2005



(43) International Publication Date  
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number  
**WO 2004/043904 A1**

(51) International Patent Classification<sup>7</sup>: **C07C 217/64**,  
C07D 333/56, A61P 25/24, 25/18, 25/06, A61K 31/381,  
31/137

(21) International Application Number:  
PCT/US2003/031514

(22) International Filing Date: 24 October 2003 (24.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/424,117 5 November 2002 (05.11.2002) US

(71) Applicant (for all designated States except US): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BOULET, Serge, Louis** [CA/US]; 10813 Windemere Boulevard, Fishers, IN 46038 (US). **FILLA, Sandra, Ann** [US/US]; 1542 Arborwoods Drive, Brownsburg, IN 46112 (US). **GALLAGHER, Peter, Thaddeus** [GB/GB]; Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire RG21 2XA (GB). **HUDZIAK, Kevin, John** [US/US]; 5944 Magnificent Lane, Indianapolis, IN 46234 (US). **JOHANSSON, Anette, Margareta** [SE/US]; 6350 Brokenhurst Road, Indianapolis, IN 46220 (US). **KARANJAWALA, Rushad, E.** [US/US]; 9732 Autumn Way, Zionsville, IN 46077 (US). **MASTERS, John, Joseph** [US/US]; 12047 Flint Stone Court, Fishers, IN 46038 (US). **MATASSA, Victor** [GB/DE]; Graffinity Pharmaceuticals, Im Neuenheimer Feld 519, 69120 Heidelberg (DE). **MATHES, Brian, Michael** [US/US]; 5335 Cotton Bay Drive West, Indianapolis, IN 46254 (US). **RATHMELL, Richard, Edmund** [GB/GB]; Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire RG21 2XA (GB). **WHATTON,**

**Maria, Ann** [GB/GB]; Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire RG21 2XA (GB). **WOLFE, Chad, Nolan** [US/US]; 16096 Tenor Way, Noblesville, IN 46060 (US).

(74) Agents: **WELCH, Lawrence, T.** et al.; Eli Lilly and Company, P.O. Box 6288, Indianapolis, IN 46206-6288 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

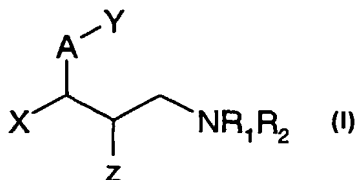
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

#### Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,

[Continued on next page]

(54) Title: 3-ARYLOXY/THIO-3-SUBSTITUTED PROPANAMINES AND THEIR USE IN INHIBITING SEROTONIN AND NOREPHINEPHRINE REUPTAKE



(57) Abstract: There is provided a compound of formula (I) wherein A is selected from -O- and -S-; X is selected from C<sub>2</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl and C<sub>4</sub>-C<sub>8</sub> cycloalkylalkyl, each of which may be optionally substituted with up to 3 substituents each independently selected from halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkyl-S(O)<sub>n</sub>- where n is 0, 1 or 2, -CF<sub>3</sub>, -CN and -CONH<sub>2</sub>; Y is selected from phenyl, naphthyl, dihydrobenzothienyl, benzothiazolyl, benzoisothiazolyl, quinolyl, isoquinolyl, naphthyridyl, thienopyridyl, indanyl, 1,3-benzodioxolyl, benzothienyl, indolyl and benzofuranyl, each

of which may be optionally substituted with up to 4 or, where possible, 5 substituents each independently selected from halo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkyl-S(O)<sub>n</sub>- where n is 0, 1 or 2, nitro, acetyl, -CF<sub>3</sub>, -SCF<sub>3</sub> and cyano; and when Y is indolyl it may be substituted or further substituted by an N-substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl; Z is selected from H, OR<sub>3</sub> or F, wherein R<sub>3</sub> is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl and phenyl C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>1</sub> and R<sub>2</sub> are each independently H or C<sub>1</sub>-C<sub>4</sub> alkyl; with the proviso that, when Z is H, then Y may not be optionally substituted phenyl or optionally substituted naphthyl.

WO 2004/043904 A1



DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY,

CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG) of inventorship (Rule 4.17(iv)) for US only

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US03/31514

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C217/64 C07D333/56 A61P25/24 A61P25/18 A61P25/06  
A61K31/381 A61K31/137

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T.L. LEMKE: "beta-Adrenergic blocking agents. alpha- and gamma-Methyl(aryloxy)propanolamines" J.MED.CHEM., vol. 24, no. 10, 1981, pages 1211-1214, XP002275394 *p. 1221, compounds 5a-f*	1,2,4, 16,17, 39-43
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 30 November 1988 (1988-11-30), XP002275395 Database accession no. BRN: 1463192 AND 1468893 abstract  -/-	1,2,8, 32,33, 40-43

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

30 March 2004

Date of mailing of the international search report

16/04/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Österle, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/31514

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	& MNDZHOYAN ET AL: IZV.AKAD.NAUK.ARM.SSR.KHIM.NAUKI, vol. 15, 1962, page 185, ----- EP 0 373 836 A (LILLY CO ELI) 20 June 1990 (1990-06-20)  the whole document	1-17, 26-31, 39-52
Y	US 5 776 969 A (JAMES STEVEN PARKER) 7 July 1998 (1998-07-07)  the whole document	1-17, 26-31, 39-52
Y	US 5 023 269 A (ROBERTSON DAVID W ET AL) 11 June 1991 (1991-06-11)  the whole document	1-17, 26-31, 39-52
P,X	WO 02/094262 A (RATHMELL RICHARD EDMUND ; FAGAN MARIA ANN (GB); GALLAGHER PETER THADDE) 28 November 2002 (2002-11-28) cited in the application the whole document	1-17, 26-31, 39-52
A	EP 0 814 084 A (LILLY CO ELI) 29 December 1997 (1997-12-29)  the whole document	1-17, 26-31, 39-52
A	US 4 229 449 A (MELLONI PIERO ET AL) 21 October 1980 (1980-10-21) cited in the application the whole document	1-17, 26-31, 39-52

Continuation of Box I.1

Although claims 49-52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

-----

Continuation of Box I.2

Claims Nos.: 1-15 (in part), 18-25, 32-38 and 39-52 (in part)

Present claims 1-52 relate to an extremely large number of possible compounds/compositions/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/compositions/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/compositions/methods supported by examples, e.g. compounds in which Y=unsubstituted or substituted phenyl or benzothienyl.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/31514

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 49-52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-15 (in part), 18-25, 32-38 and 39-52 (in part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP03/31514

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0373836	A	20-06-1990	US 4902710 A AT 102920 T CA 2005173 A1 DE 68913930 D1 DE 68913930 T2 EP 0373836 A1 JP 2218661 A	20-02-1990 15-04-1994 14-06-1990 21-04-1994 14-07-1994 20-06-1990 31-08-1990
US 5776969	A	07-07-1998	NONE	
US 5023269	A	11-06-1991	US 4956388 A AT 57924 T AU 591007 B2 AU 8266087 A CA 1302421 C CN 87108175 A , B CY 1682 A DE 3765919 D1 DK 664887 A EG 18230 A EP 0273658 A1 GR 3001207 T3 HK 69693 A HU 47561 A2 IL 84863 A JP 2549681 B2 JP 63185946 A KR 9603808 B1 MX 9845 A NZ 222980 A PH 26556 A PT 86389 A , B SG 114992 G SU 1598865 A3 ZA 8709472 A	11-09-1990 15-11-1990 23-11-1989 23-06-1988 02-06-1992 06-07-1988 10-10-1993 06-12-1990 23-06-1988 30-10-1992 06-07-1988 30-07-1992 30-07-1993 28-03-1989 29-03-1992 30-10-1996 01-08-1988 22-03-1996 01-12-1993 28-11-1989 19-08-1992 01-01-1988 29-01-1993 07-10-1990 30-08-1989
WO 02094262	A	28-11-2002	CA 2445010 A1 EP 1397129 A1 WO 02094262 A1	28-11-2002 17-03-2004 28-11-2002
EP 0814084	A	29-12-1997	AT 203990 T AU 3401797 A CA 2257962 A1 DE 69706000 D1 DE 69706000 T2 DK 814084 T3 EP 0814084 A1 ES 2160894 T3 GR 3037072 T3 HK 1008525 A1 JP 2000513358 T PT 814084 T WO 9748698 A1 US 5912256 A	15-08-2001 07-01-1998 24-12-1997 13-09-2001 04-04-2002 08-10-2001 29-12-1997 16-11-2001 31-01-2002 15-03-2002 10-10-2000 30-11-2001 24-12-1997 15-06-1999
US 4229449	A	21-10-1980	IT 1111676 B IT 1160301 B IT 1160302 B	13-01-1986 11-03-1987 11-03-1987

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 83/31514

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4229449	A	IT 1101724 B	07-10-1985
		AT 371813 B	10-08-1983
		AT 40679 A	15-12-1982
		AU 525954 B2	09-12-1982
		AU 4332779 A	26-07-1979
		BE 873596 A1	19-07-1979
		BG 61056 B2	30-09-1996
		CA 1128942 A1	03-08-1982
		CH 650245 A5	15-07-1985
		CS 207696 B2	31-08-1981
		CS 9104133 A3	13-05-1992
		CY 1172 A	10-06-1983
		DE 2901032 A1	02-08-1979
		DK 22679 A ,B,	21-07-1979
		FI 790177 A ,B,	21-07-1979
		FR 2442839 A1	27-06-1980
		FR 2430412 A1	01-02-1980
		GB 2014981 A ,B	05-09-1979
		HK 5783 A	08-02-1983
		IE 47727 B1	30-05-1984
		IL 56369 A	31-05-1984
		JP 1504458 C	28-06-1989
		JP 54148739 A	21-11-1979
		JP 63031455 B	23-06-1988
		KE 3243 A	03-12-1982
		MY 1884 A	31-12-1984
		NL 7900412 A ,B,	24-07-1979
		NO 790205 A ,B,	23-07-1979
		NZ 189418 A	16-03-1981
		SE 446727 B	06-10-1986
		SE 7900498 A	21-07-1979
		SI 7910096 A8	31-10-1996
		US 4271160 A	02-06-1981
		YU 9679 A1	31-12-1983
		ZA 7900215 A	26-03-1980
		AT 376964 B	25-01-1985
		AT 419781 A	15-06-1984
		CS 207697 B2	31-08-1981
		MX 9203112 A1	01-07-1992
		SU 980617 A3	07-12-1982
		HU 178214 B	28-03-1982
		SU 944500 A3	15-07-1982